Second Primary Cancers in Patients with Invasive and In Situ Squamous Cell Skin Carcinoma, Kaposi Sarcoma, and Merkel Cell Carcinoma: Role for Immune Mechanisms?

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Second primary cancers (SPCs) are becoming a common cancer entity, which may interfere with survival in relatively benign first primary cancers. We examined the hypothesis that immune dysfunction may contribute to SPCs by assessing SPCs associated with known immune responsive skin cancers, invasive and in situ squamous cell carcinoma, Kaposi sarcoma, and Merkel cell carcinoma. Cancers were identified from the Swedish Cancer Registry from the year 1958 to 2015. Standardized relative risks were calculated bidirectionally for any SPC after skin cancer and for skin cancer as SPC. Over 80,000 first primary cancers were identified for each invasive and in situ squamous cell carcinoma of the skin. Bidirectional increased risks were observed for 26 cancers associated with invasive skin cancer; the Spearman rank correlation was 0.72 ($P = 4.6 \times 10^{-5}$). The highest bidirectional relative risks were for invasive and in situ skin cancer as SPCs (14.59 and 16.71, respectively). Remarkably high risks for second in situ squamous cell carcinoma of the skin were found after Kaposi sarcoma (685.68) and Merkel cell carcinoma (117.23). The high systematic bidirectional risks between immune responsive skin cancers and most other cancers suggest that immune suppression is a key mechanism contributing to an increased risk of SPCs.

Journal of Investigative Dermatology (2020) **140,** 48–55; doi:10.1016/j.jid.2019.04.031

INTRODUCTION

Squamous cell carcinoma (SCC) of the skin is among the most frequently diagnosed form of cancer in fair-skinned populations, and whose incidence rates have increased in recent years (Green and Olsen, 2017; Hussain et al., 2010; Rees et al., 2014). In addition to invasive SCC, intraepithelial (in situ) SCCs of the skin, also known as Bowen's disease, are also common (Hussain et al., 2010). Although generally nonfatal, treatment for SCC can be potentially disfiguring and the large volume of patients affected by SCC contributes to vast health care costs (Green and Olsen, 2017). Cumulative exposure to ultraviolet radiation is the main established risk factor for SCC. Other risk factors include sun-sensitive skin, immunosuppression, exposure to arsenic, glucocorticoids and polycyclic hydrocarbons, and possibly smoking and cutaneous papillomavirus infections (Green and Olsen, 2017; IARC, 2012b). Kaposi sarcoma (KS) and Merkel cell carcinoma (MCC) are virus-associated tumors that affect the skin and soft tissues (Zur Hausen, 2009). Human herpesvirus 8 is considered a necessary but insufficient cause of KS, whereas Merkel cell polyomavirus is the cause of MCC (Zur Hausen, 2009). In Sweden, both KS and MCC are diseases that typically occur among elderly people, mainly men, but in populations with high prevalence of HIV infection, KS and MCC also affect younger individuals (Hussain et al., 2010; Ji and Hemminki, 2007). Alike skin SCC, KS and MCC are more common in immune deficiency conditions and immunosuppressed patients, and the risks for KS may be 200-fold (Hemminki et al., 2012; Lanoy et al., 2010; Zur Hausen, 2009).

Skin SCC is not recorded by most national cancer registries, and thus, population-based epidemiology concerning this common cancer, especially the in situ SCC, is limited compared with many other cancers. Nevertheless, a systematic review was able to summarize results from 10 studies reporting on second primary cancers (SPCs) after SCC and found significant increases for cancers of the salivary glands, lip, mouth, pharynx, and lung, and for melanoma and non-Hodgkin lymphoma (Wheless et al., 2010). Previous results

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Abbreviations: KS, Kaposi sarcoma; MCC, Merkel cell carcinoma; RR, relative risk; SCC, squamous cell carcinoma; SPC, second primary cancer; UAT, upper aerodigestive tract

Received 11 February 2019; revised 15 April 2019; accepted 17 April 2019; accepted manuscript published online 6 July 2019; corrected proof published online 6 September 2019

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Table 1. Summary of the Cohort Followed

Summary of Cases	Values
Total number of individuals followed	16.1 million
Number of invasive skin cancer	71,938
Median age at diagnosis, y	75 (64–81)[1]
SPCs after invasive skin cancer	25,108
Median follow-up time until SPC diagnosis, y	2.5 (1–6)
Number of in situ skin cancer	82,556
Median age at diagnosis, y	73 (65–80)
SPCs after in situ skin cancer	18,105
Median follow-up time until SPC diagnosis, y	5 (2–10)

Histologic Classification	Invasive Squamous Cell Carcinoma	In Situ Squamous Cell Carcinoma	Kaposi Sarcoma	Merkel Cell Carcinoma
PAD identification codes	146	144	446	566
Number of cancer diagnosis	71,938	82,556	597	1,011
Number of skin SPCs among: all invasive skin cancer	9,148	9,340	57	38
all in situ skin cancer	5,284	18,559	28	7
squamous cell carcinoma	8,655	7,682	13	24
Kaposi sarcoma	12	35	38	0
Merkel cell carcinoma	19	11	0	5

Abbreviations: PAD, histology code; SPC, second primary cancer; y, years.
[1]Values in square bracket indicated interquartile range

from Swedish studies suggested that the risks for SPCs might be somewhat similar between invasive and in situ SCC (Hemminki and Dong, 2000). Data on SPCs related to MCC and KS are sparse but some associations have been reported, including with non-Hodgkin lymphoma and chronic lymphocytic leukemia (Kaae et al., 2010; Koljonen et al., 2015; Tadmor et al., 2012; Zheng et al., 2019). Invasive and in situ SCCs also share familial risks. SCC is a manifestation in some very rare cancer syndromes affecting DNA repair (xeroderma pigmentosum and Fanconi anemia subtypes), chromosomal instability (Bloom and Werner syndrome), transforming growth factor-β signaling, telomere maintenance, and several other pathways (Green and Olsen, 2017; Rahman, 2014). Genome-wide association studies on SCC have identified 20 low-risk loci, many of which function in pigmentation, immune regulation, or oncogenic pathways (Green and Olsen, 2017).

In the present study, we focused on assessing risks of SPCs in patients with invasive and in situ skin SCC, KS, and MCC, and reciprocally, risk of these cancers as SPCs after any cancer. We anticipate that the bidirectional results will help to understand the underlying causes for SPCs. We wanted to focus, in particular, on the recent challenging bidirectional results on SPCs associated with myeloid neoplasms and non-Hodgkin lymphoma that suggested that immunosuppression contributed to the risk of SPC (Chattopadhyay et al., 2018a; Chattopadhyay et al., 2018b). As immunosuppression is the shared risk factor for SCC skin cancer, KS, and MCC, we expect our results to be highly informative concerning immune mechanisms in SPCs (Harms et al., 2018; IARC, 2012a; Rama and Grinyó, 2010; Rangwala and Tsai, 2011). Recent data also suggest that these cancers are responsive to immunotherapy (Colunga et al., 2018; Galanina et al., 2018; Migden et al., 2018). We utilized data from the nationwide Swedish Cancer Registry covering the years 1958 through to 2015.

RESULTS

Of the total 16.1 million individuals followed, 82,205 developed invasive skin cancer and 82,556 developed in situ skin cancer by the end of 2015 (Table 1). Among the people with invasive skin cancer, 25,108 later developed SPC with a median time to SPC of 2.5 years. For in situ skin cancer patients, the number of SPC diagnosis was 18,105 with a longer time to SPC of 5 years. Median age at SPC diagnosis was 75 after invasive skin cancer and 73 years after in situ skin cancer. Age of diagnosis (median [interquartile range]) of invasive SCC as SPC was 82 years (73–86) and for in situ SCC it was 79 years (72–84). Time to invasive SCC as SPC was 7 years (3–13) and time to in situ SCC as SPC was 7 years (3–15). Age-standardized incidence rates of SCC are shown in Supplementary Figure S1. During the study period the incidence of invasive SCC increased about 10 times and it increased even more for in situ SCC, for which the rate surpassed the rate of invasive SCC at around 1990.

Bidirectional risks for invasive skin SCC with any cancer are shown in Table 2. Column A shows the risks of SPC after skin cancer. SPC of the in situ skin and invasive SCCs showed the highest risks of 16.71 and 14.59, respectively. The overall risk of SPC other than skin cancer was 1.41, with 23 SPCs of significantly increased risk. Among the highest risks of individual SPCs, the relative risks (RRs) increased more than 3-fold for cancers of the upper aerodigestive tract (UAT; RR of 4.42), nose (3.09), and for melanoma (3.81), whereas anal, connective tissue, and male and female genital SPCs, and leukemia, Hodgkin and non-Hodgkin lymphoma had a more than 2-fold excess risk. In column B, with the reciprocal analyses, risks for SPC of the skin showed high risks,

Table 2. Risk of SPC after Invasive Skin SCC and Risk of Second Primary Invasive Skin SCC after Any Cancer

	A. Risk of SPCs after Invasive Skin SCC					B. Risk of Invasive Skin SCC after Any Cancer				
Cancer	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**
UAT[1]	485	**4.42**	4.04	4.84	<0.0001	897	**5.65**	5.29	6.04	<0.0001
Esophagus[1]	104	**1.75**	1.44	2.12	<0.0001	33	**1.65**	1.17	2.32	0.004
Stomach[1]	388	**1.56**	1.41	1.72	<0.0001	153	**1.19**	1.02	1.40	0.031
Small intestine	34	1.34	0.96	1.89	0.0861	39	**1.68**	1.23	2.30	0.0012
Colorectum[1]	1,185	**1.47**	1.39	1.56	<0.0001	1,377	**1.51**	1.43	1.59	<0.0001
Anus[1]	33	**2.69**	1.91	3.80	<0.0001	32	**2.17**	1.53	3.07	<0.0001
Liver	228	**1.17**	1.03	1.33	0.0184	39	0.78	0.57	1.07	0.1187
Pancreas	203	1.14	0.99	1.31	0.063	26	**0.64**	0.44	0.94	0.0227
Nose[1]	26	**3.09**	2.09	4.56	<0.0001	51	**5.02**	3.81	6.60	<0.0001
Lung[1]	712	**1.84**	1.71	1.98	<0.0001	190	**1.27**	1.10	1.46	0.0011
Breast[1]	643	**1.35**	1.25	1.46	<0.0001	1,627	**1.65**	1.57	1.74	<0.0001
Cervix	31	1.25	0.88	1.78	0.2107	163	**1.75**	1.50	2.04	<0.0001
Endometrium[1]	142	**1.39**	1.18	1.64	0.0001	507	**1.73**	1.58	1.89	<0.0001
Ovary[1]	95	**1.42**	1.16	1.73	0.0007	138	**1.30**	1.10	1.53	0.0023
Other female genitals[1]	59	**2.12**	1.64	2.75	<.0001	52	**1.72**	1.31	2.25	<0.0001
Prostate[1]	1,829	**1.20**	1.15	1.26	<0.0001	2,884	**1.53**	1.47	1.59	<0.0001
Testis	5	1.77	0.73	4.27	0.2055	46	**2.39**	1.79	3.19	<0.0001
Other male genitals[1]	31	**2.30**	1.61	3.29	<0.0001	39	**1.90**	1.39	2.61	<0.0001
Kidney[1]	200	**1.54**	1.34	1.77	<0.0001	197	**1.37**	1.19	1.57	<0.0001
Urinary bladder[1]	542	**1.83**	1.68	1.99	<0.0001	691	**1.72**	1.59	1.85	<0.0001
Melanoma[1]	587	**3.81**	3.51	4.14	<0.0001	1,190	**3.89**	3.67	4.12	<0.0001
Skin (in situ)[1]	7,682	**16.71**	16.30	17.14	<0.0001	5,284	**8.33**	8.09	8.58	<0.0001
Skin (invasive)										
Squamous cell[1]	8,655	**14.59**	14.25	14.93	<0.0001					
Kaposi sarcoma[1]	13	**2.69**	1.55	4.67	0.0004	52	**8.93**	6.81	11.73	<0.0001
Merkel cell[1]	24	**3.98**	2.64	6.02	<0.0001	26	**5.41**	3.68	7.94	<0.0001
Eye[1]	17	**1.65**	1.02	2.67	0.0393	33	**1.57**	1.12	2.21	0.0095
Nervous system	94	1.08	0.88	1.32	0.4725	157	**1.22**	1.05	1.43	0.0113
Thyroid gland	33	1.28	0.91	1.80	0.1588	73	**1.26**	1.00	1.59	0.0463
Endocrine glands	41	0.83	0.61	1.13	0.2292	223	**1.37**	1.20	1.56	<0.0001
Bone	6	1.45	0.65	3.24	0.3667	13	1.57	0.91	2.70	0.1042
Connective tissue[1]	78	**2.55**	2.03	3.19	<0.0001	97	**2.40**	1.97	2.93	<0.0001
NHL[1]	445	**2.55**	2.32	2.80	<0.0001	840	**5.02**	4.69	5.38	<0.0001
Hodgkin lymphoma[1]	29	**2.18**	1.51	3.15	<0.0001	91	**5.83**	4.75	7.16	<0.0001
Multiple myeloma[1]	109	**1.25**	1.03	1.50	0.0228	106	**1.84**	1.52	2.22	<0.0001
Leukemia[1]	355	**2.15**	1.93	2.38	<0.0001	867	**6.14**	5.74	6.57	<0.0001
CUP[1]	366	**1.58**	1.43	1.75	<0.0001	115	**1.60**	1.33	1.92	<0.0001
All (without skin)	9,731	**1.41**	1.38	1.44	<0.0001	12,989	**1.98**	1.94	2.02	<0.0001

Boldface indicates that 95% CIs do not include RR of 1.00.

Abbreviations: CI, confidence interval; CUP, carcinoma of unknown primary; NHL, non-Hodgkin lymphoma; RR, relative risk; SPC, second primary cancer; SCC, squamous cell carcinoma; UAT, upper aerodigestive tract.

[1]Both bidirectional RRs significantly increased.

including RR of 8.93 for second KS and 5.41 for second MCC. The overall risk of SPC other than concordant skin was 1.98, with 29 significantly increased risks for SPC of the skin. More than 5-fold increase in risk for SPC of the skin was found when UAT (5.65) and nasal (5.02) cancers, Hodgkin (5.83) and non-Hodgkin lymphoma (5.02), and leukemia (6.14) were first cancers.

Bidirectional risks of SPC after in situ skin SCC (column A) and of in situ skin SCC as SPC (column B) are shown in Table 3. SPCs were increased at five non-skin sites, with an overall RR of 1.22, which was partially explained by the individual RRs that were below 1.00. The highest RRs were for melanoma (1.90) and Hodgkin lymphoma (1.66). SPC in situ SCC showed an RR of 18.84, twice as high as the RR of 9.88 for invasive skin cancer; the RR for KS was 4.45. The overall RR for in situ skin cancer as SPC was 2.00, contributed by increased risks after 25 different cancers other than skin cancers. In situ skin cancer risk was increased to 6.05 after leukemia, to 4.73 after melanoma, to 4.61 after non-Hodgkin lymphoma, and to 4.65 after Hodgkin lymphoma. Remarkably high risks for second in situ SCC cancer were found after KS (685.68) and MCC (117.23).

In Table 4, we assessed the concordance for bidirectional SPC risks from Tables 2 and 3, (shown by superscript number 1). In Table 2, RRs for 26 SPC pairs were both significant, that is, remarkably high RR of 4.42 for UAT cancer as SPC and 5.65 for invasive skin cancer after UAT cancer, for nasal

Table 3. Risk of SPC after In Situ Skin SCC and Risk of Second Primary In Situ Skin SCC after Any Cancer

	A. Risk of SPCs after In Situ Skin SCC					B. Risk of Second Primary In Situ Skin SCC after Invasive Cancer				
Cancer	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**
UAT	214	1.19	1.04	1.36	0.0121	826	**3.50**	3.27	3.75	<0.0001
Esophagus	89	0.87	0.71	1.08	0.2046	29	1.12	0.78	1.61	0.5384
Stomach	272	**0.73**	0.65	0.82	<0.0001	180	1.15	1.00	1.33	0.0573
Small intestine	43	0.99	0.73	1.34	0.9594	53	1.55	1.18	2.03	0.0015
Colorectum	1,252	0.97	0.92	1.03	0.292	1,795	**1.49**	1.42	1.56	<0.0001
Anus	18	0.88	0.55	1.40	0.5778	47	**2.40**	1.80	3.19	<0.0001
Liver	211	**0.65**	0.57	0.75	<0.0001	68	1.09	0.86	1.38	0.4761
Pancreas	246	**0.83**	0.73	0.94	0.0028	42	0.84	0.62	1.14	0.268
Nose	16	1.18	0.72	1.94	0.5049	37	**2.56**	1.85	3.53	<0.0001
Lung	603	**0.88**	0.81	0.96	0.0023	313	**1.50**	1.34	1.67	<0.0001
Breast	918	0.96	0.90	1.03	0.258	2,952	**1.60**	1.54	1.66	<0.0001
Cervix	34	0.67	0.48	0.94	0.0199	271	**1.43**	1.27	1.61	<0.0001
Endometrium	172	**0.76**	0.66	0.89	0.0004	851	**1.57**	1.46	1.68	<0.0001
Ovary	139	0.93	0.78	1.09	0.3629	297	**1.45**	1.29	1.62	<0.0001
Other female genitals	63	1.15	0.90	1.48	0.2589	77	**1.60**	1.28	2.00	<0.0001
Prostate	1,508	**0.85**	0.80	0.89	<0.0001	3,224	**1.82**	1.75	1.89	<0.0001
Testis						66	**2.13**	1.67	2.71	<0.0001
Other male genitals	15	0.93	0.56	1.55	0.7761	37	**1.71**	1.24	2.36	0.0011
Kidney	180	**0.82**	0.70	0.94	0.0064	324	**1.49**	1.33	1.66	<0.0001
Urinary bladder	426	**0.86**	0.78	0.94	0.0015	924	**1.54**	1.44	1.64	<0.0001
Melanoma[1]	476	**1.90**	1.73	2.08	<0.0001	2,132	**4.73**	4.53	4.94	<0.0001
SCC (in situ) [1]	18,559	**18.84**	18.52	19.16	<0.0001					
Skin (invasive)										
SCC[1]	5,037	**9.88**	9.59	10.19	<0.0001	7,682	**16.71**	16.30	17.14	<0.0001
Kaposi sarcoma[1]	28	**4.45**	3.02	6.57	<0.0001	35	**685.68**	482.32	974.81	<0.0001
Merkel cell	6	1.21	0.54	2.71	0.6454	11	**117.23**	64.48	213.14	<0.0001
Eye	16	0.91	0.55	1.48	0.696	39	1.26	0.92	1.73	0.1484
Nervous system	112	**0.71**	0.59	0.86	0.0004	255	**1.29**	1.14	1.46	<0.0001
Thyroid gland	37	0.86	0.62	1.18	0.3469	117	**1.27**	1.06	1.52	0.0098
Endocrine glands	63	**0.69**	0.54	0.89	0.0039	403	**1.65**	1.50	1.82	<0.0001
Bone	7	1.01	0.48	2.13	0.9717	19	1.43	0.91	2.24	0.1181
Connective tissue[1]	70	**1.40**	1.10	1.77	0.0058	132	**2.17**	1.83	2.57	<0.0001
NHL[1]	388	**1.32**	1.19	1.45	<0.0001	1,093	**4.61**	4.34	4.90	<0.0001
Hodgkin lymphoma[1]	36	**1.66**	1.20	2.31	0.0025	124	**4.65**	3.90	5.54	<0.0001
Multiple myeloma	115	**0.78**	0.65	0.93	0.0067	160	**2.10**	1.80	2.45	<0.0001
Leukemia[1]	322	**1.20**	1.08	1.35	0.0009	1,156	**6.05**	5.71	6.41	<0.0001
CUP	386	1.00	0.90	1.10	0.9604	127	**1.40**	1.18	1.67	0.0001
All (without skin)	8,447	**1.22**	1.18	1.24	<0.0001	18,173	**2.00**	1.96	2.03	<0.0001

Boldface indicates that 95% CIs do not include RR of 1.00.

Abbreviations: CI, confidence interval; CUP, carcinoma of unknown primary; NHL, non-Hodgkin lymphoma; RR, relative risk; SPC, second primary cancer; SCC, squamous cell carcinoma; UAT, upper aerodigestive tract.

[1]Both bidirectional RRs significantly increased.

cancer (3.09 and 5.02) and for melanoma (3.81 and 3.89). The Spearman rank correlation was 0.72 ($P = 4.6 \times 10^{-5}$) for these 26-paired RRs (Table 4). The correlation was even higher for the 29-paired RRs between second invasive and in situ skin cancers (rho = 0.90, $P = 4.2 \times 10^{-11}$). Some of the other shown correlations were also highly significant.

SPC risks after KS and risk of second primary KS after other cancers are reported in the top panel of Table 5 for cancers other than skin cancer; the overall risks were 1.71 and 1.88, respectively. Despite the small case number, a bidirectional increase in risk was observed for all hematological cancers: Hodgkin lymphoma (21.00 and 9.33), non-Hodgkin lymphoma (5.95 and 7.09), multiple myeloma (3.73 and 6.31), and leukemia (2.59 and 3.75). Among other cancers, SPC of liver (2.31) and cancer of unknown primary (2.43) had excess risk after KS. Second primary KS was observed with an excess risk after lung (2.68), testicular (8.65), bladder (2.09), and connective tissue cancers (14.87).

MCC was associated with a high overall risk of subsequent SPC, RR of 1.90, and 1.81 for MCC as SPC (Table 6). Cancers of UAT, endocrine glands, and melanoma were associated with a bidirectional risk. Additionally, RRs for SPC of the liver (3.11), endometrium (3.10), and kidney (4.81) were increased. The reciprocal analyses showed an excess risk of second primary MCC after prostate (1.92) and bladder cancers (2.19), non-Hodgkin lymphoma (4.74), and leukemia (8.73).

Table 4. Linear Ranked Correlations among Skin SCC and Other Cancers between Pairs of First and SPCs Shown in Tables 2 and 3

	SPC after Invasive SCC	Invasive SCC as SPC	SPC after in situ SCC	In situ SCC as SPC
SPC after invasive SCC	1	—	—	—
Invasive SCC as SPC	0.72 ($P = 4.6 \times 10^{-5}$) 26	1	—	—
SPC after in situ SCC	0.89 ($P = 2.4 \times 10^{-3}$) 8	0.56 ($P = 0.15$) 8	— 1	—
In situ SCC as SPC	0.72 ($P = 1.1 \times 10^{-4}$) 24	0.90 ($P = 4.2 \times 10^{-11}$) 29	0.57 ($P = 0.20$) 7	1

Each cell represents the Spearman rho, two-tailed test *P*-value and number of cancer pairs with significantly increased RRs.
Abbreviations: RR, relative risk; SPC, second primary cancer; SCC, squamous cell carcinoma.

DISCUSSION

The present study carries out a systematic bidirectional analysis of SPCs after invasive and in situ skin cancers and of skin cancers as SPCs after any cancers. Treatment is often regarded as an important risk factor for SPC, but in the case of SPC after skin cancers, other factors need to be considered, as their treatment is primarily surgery and infrequently radiotherapy. SCC of the skin, KS, and MCC are all cancers frequently occurring in immunosuppressed individuals, and the present bidirectional analyses suggest that induced (by the tumor or treatment) or inherent immune dysfunction may be a common shared mechanism for SPC, especially for non-Hodgkin lymphoma, and for kidney, UAT (particularly lip), genital, stomach, and colorectal cancers (Harms et al., 2018; Hortlund et al., 2017; IARC, 2012a; Rama and Grinyó, 2010; Rangwala and Tsai, 2011). For example, in Table 2, a large majority (26 of 36) of bidirectional comparisons between RRs for cancer X as SPC and skin SCC as SPC after cancer X were mutually significant. Many of the correlation coefficients were high and highly significant irrespective of whether invasive or in situ SCC skin cancers were considered as first cancer or SPC. Although we cannot exclude the role of other contributing factors for SPC, no known lifestyle related risk factors are known to exert risks at such a large number of diverse cancers. Additionally, it is likely that treatment of first primary cancer contributed to the risks of skin cancer as SPC,

Table 5. Risk of SPC after KS and that of Second Primary KS after Other Invasive Cancers

	A. Risk of Invasive SPCs after KS					B. Risk of Second Primary KS after Invasive Cancers				
Cancer	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**
UAT	3	2.26	0.73	7.01	0.1576	2	1.09	0.27	4.37	0.903
Stomach	5	1.38	0.57	3.31	0.4737	3	1.58	0.51	4.91	0.4301
Colorectum	14	1.48	0.88	2.51	0.1399	12	1.37	0.77	2.43	0.2832
Liver	**6**	**2.31**	**1.04**	**5.15**	**0.0401**	0				
Pancreas	2	0.86	0.21	3.43	0.8287	0				
Lung	2	0.45	0.11	1.79	0.256	**4**	**2.68**	**1.00**	**7.18**	**0.0492**
Breast	4	1.14	0.43	3.05	0.7867	8	1.40	0.69	2.85	0.3546
Endometrium	0					4	2.40	0.89	6.48	0.0843
Prostate	21	1.06	0.69	1.63	0.7811	28	1.41	0.96	2.08	0.0803
Testis	0					**3**	**8.65**	**2.77**	**27.02**	**0.0002**
Kidney	3	1.76	0.57	5.46	0.3273	1	0.67	0.09	4.78	0.6917
Urinary bladder	4	1.20	0.45	3.20	0.7163	**8**	**2.09**	**1.04**	**4.21**	**0.0385**
Melanoma	1	0.63	0.09	4.50	0.6487	2	0.95	0.24	3.82	0.9445
Endocrine glands	1	1.59	0.22	11.30	0.6422	3	2.29	0.73	7.12	0.1535
Connective tissue	1	2.68	0.38	19.06	0.3235	**6**	**14.87**	**6.65**	**33.24**	**<0.0001**
NHL[1]	**12**	**5.95**	**3.38**	**10.48**	**<0.0001**	**10**	**7.09**	**3.79**	**13.27**	**<0.0001**
Hodgkin lymphoma[1]	**4**	**21.00**	**7.88**	**56.00**	**<0.0001**	**2**	**9.33**	**2.33**	**37.37**	**0.0016**
Multiple myeloma[1]	**4**	**3.73**	**1.40**	**9.93**	**0.0085**	**4**	**6.31**	**2.36**	**16.87**	**0.0002**
Leukemia[1]	**5**	**2.59**	**1.08**	**6.22**	**0.0335**	**5**	**3.75**	**1.55**	**9.05**	**0.0033**
CUP	**7**	**2.43**	**1.16**	**5.10**	**0.0189**	1	1.25	0.18	8.91	0.822
All (without skin)	**103**	**1.71**	**1.43**	**1.96**	**<0.0001**	**113**	**1.88**	**1.54**	**2.31**	**<0.0001**

Boldface indicates that 95% CIs do not include RR of 1.00.
Abbreviations: CI, confidence interval; CUP, carcinoma of unknown primary; KS, Kaposi sarcoma; NHL, non-Hodgkin lymphoma; RR, relative risk; SPC, second primary cancer; SCC, squamous cell carcinoma; UAT, upper aerodigestive tract.
[1]Both bidirectional RRs significantly increased.

Table 6. Risk of SPC after MCC and that of Second Primary MCC after Other Invasive Cancers

	A. Risk of Invasive SPCs after MCC					B. Risk of Second Primary MCC after Invasive Cancers				
Cancer	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**	**N**	**RR**	**Lower CI**	**Upper CI**	***P*-value**
UAT[1]	**3**	**4.04**	**1.30**	**12.54**	**0.0155**	**6**	**3.92**	**1.75**	**8.77**	**0.0009**
Colorectum	5	0.89	0.37	2.13	0.7853	12	1.25	0.71	2.23	0.4384
Liver	**4**	**3.11**	**1.17**	**8.28**	**0.0233**	0				
Pancreas	2	1.74	0.43	6.94	0.4354	0				
Lung	4	1.55	0.58	4.12	0.3838	2	1.42	0.35	5.70	0.6207
Breast	2	0.46	0.11	1.84	0.2709	16	1.25	0.76	2.08	0.3796
Cervix	0					1	0.85	0.12	6.04	0.8694
Endometrium	**3**	**3.10**	**1.00**	**9.62**	**0.0499**	6	1.55	0.69	3.48	0.2902
Prostate	9	1.13	0.59	2.16	0.7234	**28**	**1.92**	**1.28**	**2.87**	**0.0016**
Kidney	**4**	**4.81**	**1.81**	**12.82**	**0.0017**	**0**				
Urinary bladder	1	0.47	0.07	3.35	0.4525	**9**	**2.19**	**1.13**	**4.23**	**0.0204**
Melanoma[1]	**7**	**6.05**	**2.89**	**12.70**	**<0.0001**	**10**	**3.30**	**1.76**	**6.18**	**0.0002**
Nervous system	1	1.72	0.24	12.18	0.5895	2	1.54	0.38	6.18	0.5426
Endocrine glands[1]	**4**	**11.78**	**4.42**	**31.39**	**<0.0001**	**7**	**4.04**	**1.91**	**8.53**	**0.0002**
NHL	3	2.31	0.74	7.15	0.1479	**8**	**4.74**	**2.35**	**9.54**	**<0.0001**
Leukemia	3	2.59	0.83	8.02	0.0999	**12**	**8.73**	**4.92**	**15.50**	**<0.0001**
CUP	4	2.33	0.87	6.21	0.0907	**0**				
All (without skin)	**66**	**1.90**	**1.68**	**2.17**	**<0.0001**	**121**	**1.81**	**1.48**	**2.21**	**<0.0001**

Boldface indicates that 95% CIs do not include RR of 1.00.

Abbreviations: CI, confidence interval; CUP, carcinoma of unknown primary; MCC, Merkel cell carcinoma; NHL, non-Hodgkin lymphoma; RR, relative risk; SPC, second primary cancer; SCC, squamous cell carcinoma; UAT, upper aerodigestive tract.

[1]Both bidirectional RRs significantly increased.

which is probably the main explanation for the higher overall risks for skin cancer as SPC (column B in Tables 2 and 3) than for any SPC after skin cancer.

Limitations of the study include lack of data on individuals who have been immunosuppressed for medical reasons. A recent Swedish study used medical records from 1964 onwards and identified a total of 12,400 organ transplant recipients who had been diagnosed with 990 non-melanoma skin cancers (Hortlund et al., 2017). This is a modest proportion of the 82,000 SCC skin cancers of the present study. Immune suppression because of HIV may also lead to a spectrum of cancers, but the number of known HIV patients is estimated at 7,000 in the total population of 10 million Swedes, and with the current mediation, cancer risk is controlled in these patients (https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/living-conditions-and-lifestyle/hiv-and-stis/). Another problem, related to the study design, is surveillance bias, which is very difficult to control (Hemminki et al., 2017). However, it has not reached magnitudes of risk found in the present study and it diminishes when the time between first medical contact and the diagnostic contact is extended. Finally, although targeted therapies using drugs such as BRAF inhibitors may have indications in SCC treatment, it is unclear whether such treatments have been introduced in Sweden.

What is known about mechanisms of SPCs not related to therapy or shared environmental and/or lifestyle factors? Immunosuppressed organ transplantation patients have an increased risk of KS (up to 200-fold), SCC in the skin, oral cavity, and pharynx (i.e., parts of UAT), and of non-Hodgkin lymphoma and MCC (some 20-fold), and a somewhat lower but still increased risk of kidney cancer, melanoma, leukemia, and anogenital cancers (some 5-fold) (Birkeland et al., 1995; Hortlund et al., 2017; Rama and Grinyó, 2010; Wimmer et al., 2007). An increased incidence of certain viral-associated cancers in immunosuppressed populations is associated with viral reactivation, which is common in SCC, non-Hodgkin lymphoma, KS, and MCC (Rangwala and Tsai, 2011); these cancers are also increased in HIV infected populations (Hessol et al., 2018). Anogenital cancers are associated with human papillomavirus infection, particularly related to the alpha genus of mucosal human papillomavirus types 16 and 18 (Oh and Weiderpass, 2014; Zur Hausen, 2009). Of note, cervical cancer was only increased in some analyses, whereas other female genital cancers showed higher risks. The reason may be a much lower diagnostic age of cervical cancer compared with most of all other cancers. In skin, SCC the beta genus human papillomavirus may be playing a role, whereas ultraviolet irradiation would be an example of a non-infective mechanism (Bouwes Bavinck et al., 2018; IARC, 2012a). In Hodgkin and non-Hodgkin lymphoma, Epstein-Barr virus has been proposed to be a key infective causative agent (Schäfer et al., 2015). KS-associated herpes virus has a wide tropism including B cells, endothelial cells, fibroblasts, and epithelial cells, whereas for MCC papilloma virus the tropism is not well known (Schäfer et al., 2015). For these SPCs, the first primary cancer, or its treatment, may suppress immune function in other parts of the body and facilitate viral reactivation. mTOR inhibitors have been used with variable success to intervene with viral reactivation (de Fijter, 2017).

However, for many other SPCs, an infective etiology is not known, but first primary cancers may negatively influence immune function through chronic inflammation and suppression of cellular defense mechanisms, which may mimic iatrogenic immune suppression (Friman et al., 2016).

In order for tumors to evade immune surveillance, they need mechanisms to suppress the immune response (Munn and Bronte, 2016). For example, NF-κB signaling is a master regulator of cancer-associated chronic inflammation, contributing to immunosuppression through induction of proinflammatory mediators and activation of immune suppressor cells (Schreiber et al., 2005; Taniguchi and Karin, 2018; Wang and DuBois, 2015). Myeloid-derived suppressor cells, tumor-associated macrophages, N2 neutrophils, $CD8^+$ suppressors, and regulatory T cells can produce chemokines, cytokines, growth factors, and proteases, which can contribute to immune response and its suppression (Shalapour and Karin, 2015). Consequently, immunotherapy is a promising approach for the treatment of skin tumor types considered here, and as it aims at reversing the above processes, it will be exciting to observe whether the risk of SPCs decreases (Colunga et al., 2018; Galanina et al., 2018; Migden et al., 2018; Nghiem et al., 2016).

Overall, the results showed that the risks for SPC were higher after invasive SCC compared with in situ skin SCC; and this was true for each SPC, with exception of in situ skin cancer and KS. The reason may be that in situ lesions are likely to be small and less immunosuppressive than invasive skin cancers, and consequently, the median time to SPC was two times longer after in situ than after invasive first primary cancer. Curiously, the RRs for many SPCs were significantly below 1.00 after in situ skin cancer for unknown reasons. RRs for skin cancer as SPC were equal for invasive and in situ SPC, which appeared not to depend on individual first cancers. The exceptions were RRs for SPCs of the skin, which were higher for in situ SCCs than for invasive types, and particularly after KS (685.68 vs. 8.93) and MCC (117.23 vs. 5.41). The reason for this difference may be that the patients diagnosed with KS and MCC are under surveillance, particularly for skin lesions, whereby early tumors are primarily detected.

KS and MCC are rare cancers, but high risks of KS have been observed in HIV infected persons (Hessol et al., 2018). In the present analysis, we showed high bidirectional risks between KS and all hematological malignancies. The KS-associated human herpesvirus 8 is also known to cause rare primary effusion lymphoma and multicentric Castelman disease, but these are too rare to alone explain the associations with hematological malignancies (IARC, 2012a). MCC was increased as SPC after hematological malignancies, but bidirectional associations were observed with UAT cancer, melanoma, and endocrine gland tumors.

In conclusion, the high systematic bidirectional risks between skin cancers, known to be associated with immunosuppression, and most other cancers suggest that immunologic factors are key mechanisms contributing to an increased risk of SPCs. Of note, such epidemiologic data would immediately suggest that immunotherapy could be an attractive treatment option for not only skin cancers (Colunga et al., 2018; Galanina et al., 2018; Migden et al., 2018; Nghiem et al., 2016) but also SPCs arising in skin cancer patients.

MATERIALS AND METHODS

Data for our study were obtained from the Swedish Family-Cancer Database, which includes information on the residents of Sweden organized in families (Hemminki et al., 2010). Individuals were linked to the Swedish cancer register, cause of death register, migration register, and population census with a unique identifier, and were queried for first and any subsequent primary cancers (Hemminki et al., 2010). The database records cancers according to the international classification of diseases, seventh and later revisions; the code for skin cancer was 201. Until the end of 2015, more than 2.1 million cancers were recorded among 16.1 million individuals. From this data, we identified all individuals who were diagnosed with in situ skin cancer and invasive SCC, KS, and MCC with histologic identifier (WHO/HS/CANC/24.1 Histology Code, 'PAD') 144, 146, 446, and 566, respectively. If two of these cancers were reported synchronously, the first report was considered; in rare instances when the data of diagnoses were reported on the same date, invasive SCC was considered the first cancer. All skin cancers reported to the Cancer Registry are histologically verified, as are practically all other cancers (Centre for Epidemiology, 2013). We followed all newly diagnosed in situ and invasive skin cancer patients for diagnosis of any of the 32 different invasive SPCs. The follow-up started on January 1, 1958, and terminated at diagnosis of SPC, emigration, death, or December 31, 2015, whichever occurred earliest.

SPCs diagnosed after both in situ and invasive skin cancers were investigated separately. RRs of SPCs were assessed by means of incidence rate ratios of SPC among skin cancer survivors against risk of that cancer in the general population. For the bidirectional analyses, RRs for skin cancers were calculated as SPCs after any primary cancer. Person-years and SPCs were categorized according to age (5-year bands), sex, socioeconomic index (six groups), region (four groups), and calendar year. For the estimation of RRs, Poisson regression was used after a point process and corresponding confidence intervals for 5% level of significance. Fixed effects generalized linear multivariate model was used with the aforementioned regressors, including age group, sex, calendar period, residential area, and socioeconomic status, to adjust for potential confounding. Linear ranked correlations among skin SCC and other cancers between pairs of first and SPC were assessed by calculating Spearman rho with two-tailed test for *P*-value.

The study was approved by the Ethical Committee of Lund University, Sweden, without requirement for informed consent, and was conducted in accordance with the tenets of the Declaration of Helsinki. People could choose to opt out of the study, which was advertised in major newspapers, before the research database was constructed. The project database is located at the Center for Primary Health Care Research in Malmö, Sweden. All statistical analyses were done with SAS, version 9.4.

Data availability statement

Swedish Family-Cancer Database was used for this study. More information can be found online (https://www.socialstyrelsen.se/register/halsodataregister/cancerregistret/inenglish).

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CONFLICT OF INTEREST

AH is a shareholder in Targovax ASA and an employee and shareholder in TILT Biotherapeutics Ltd. The other authors state no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by the Deutsche Krebshilfe, Jane and Aatos Erkko Foundation, University of Helsinki, Sigrid Juselius Foundation, Finnish Cancer Organizations, and the Helsinki University Central Hospital. We thank Patrick Reilly for excellent language revision.

AUTHOR CONTRIBUTIONS

Conceptualization: KH; Data Curation: KS, JS, SC; Formal Analysis: SC, KH; Writing - Original Draft Preparation: KH, SC, AH, AF; Writing - Review and Editing: KH, SC, AH, AF, KS, JS.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2019.04.031.

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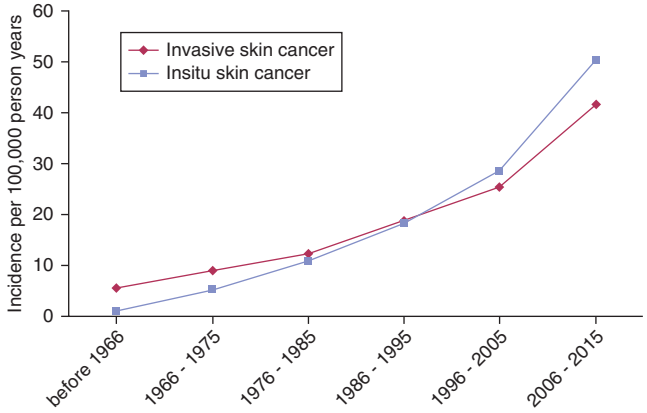

Supplementary Figure S1. Age-standardized incidence rates of invasive and in situ SCC according to the Swedish Cancer Registry. SCC, squamous cell carcinoma.